REMARKS

This invention relates to, *inter alia,* a transdermal therapeutic system ("TTS") for the therapeutic administration of calcium antagonists of the dihydropyridine type, to a process for its preparation and to its use in medicine. More specifically, Applicants discovered a TTS that will administer a calcium antagonist of the dihydropyridine type in a satisfactory manner. As indicated in Ueda, et al., U.S. Patent 5,045,553 ("Ueda") it is difficult to attain an effective drug concentration by percutaneous administration of dihydropyridine type because they are "sparingly soluble in water and, as such, can be absorbed percutaneously only to a slight extent" (col. 1, line 46-50). Applicants achieved this result by formulating the dihydropyridine calcium antagonist as a solution in an alcohol, a pyrrolidone derivative, and a saturated or unsaturated fatty acid ester of a carboxylic acid containing 8 to 16 carbon atoms and a polyhydroxy alcohol. Surprisingly, the inventive TTS administers the dihydropyridine calcium in amounts which are synergistic.

Pursuant to 37 CFR 1.136(a), Applicants petition the Director to extend the time period to file a response to the outstanding Office Action by one (1) month, i.e., up to and including July 15, 2004. A check for $110 is enclosed to cover the cost of this petition.

It is believed that no further fee is required for the consideration of this Amendment. If, however, an additional fee is due the Director is authorized to charge such fee to Deposit Account 50-0320.

The specification has been amended per the request of the Examiner.

The file of the undersigned and the office file have a different number of claims, which is apparently due to amendments made to the international applications. In order to avoid

any confusion, Applicants have cancelled all the claims and added a new set of claims. As these changes do not affect their scope, the doctrine of equivalency is not affected.

It is urged that the objection to claims 5 to 12 under 37 CFR 1.75(c) and the rejection of claims 2 and 8 to 12 under 35 USC §112, second paragraph and claims 8 under 35 USC §101 are moot and should be withdrawn.

Claims 1 to 11 stand rejected under 35 USC §103(a) for allegedly being unpatentable over U.S. Patent 4,938,395 to Chang et al. ("Chang") in view of U.S. Patent 4, 879,119 to Konno et al. ("Konno"). As Chang taken with Konno does not suggest a TTS where the active agent is in a solution, the rejection does not establish a *prima facie* case of obviousness. Moreover, these documents do not suggest the superior results exhibited by the present invention. Accordingly, reconsideration and withdrawal of this rejection is requested.

The present claims provide for a TTS where the dihydropyridine calcium antagonist is dissolved in a solution comprising a specific alcohol, a pyrrolidone derivative and a saturated or unsaturated fatty acid ester of C_8-C_{16} carboxylic acid and a polyhydric alcohol. The present invention is not a gel or a solid base.

Chang relates to a TTS device where the drug formulation containing reservoir is defined by a backing layer, a drug permeable membrane layer and a peelable liner (see Abstract). While not describing the formulation contained in the reservoir in detail, the calcium antagonist in the example is present as a gel. For example, in Example 3, the gel consisting of nicardipine-hydrochloride, Klucel HF® and a mixture of ethanol, water, glycerol and glycerol monooleate as permeation enhancer. Thus, not only does Chang fail to teach the pyrrolidone derivatives as additional enhancer (Office Action at 6), but Chang fails to teach a solution.

Contrary to the position taken in the rejection, it is respectfully urged that Konno does not correct for the deficiencies found in Chang. Konno discloses a transdermal patch where drug component is uniformly dispersed in a base mainly comprised of cacao butter, isocacao butter or a triglyceride of a vegetable saturated fatty acid having 12 to 18 carbon atoms together with a penetration enhancer. The base is present in an amount which is capable of maintaining a solid state since this is in the form of a patch (col. 3, lines 30-31) (The base of the patch ... is melted at about body temperature (col. 3, line 52)). Hence, Konno does not disclose a reservoir formulation where all the components are in a solution. As with Chang, the components are not present in a solution but rather a solid or semisolid state.

Further, Applicants respectfully disagree with the position that Konno discloses the use of N-methyl-2-pyrrolidone as an enhancer. Konno uses this compound as a solvent to dissolve the pharmaceutical agent before the solution is mixed (or "kneeded") in the molten base (see col. 2, lines 49-57 and col. 3, lines 32-38). Hence, Konno does not provide any motivation to one of ordinary skill in the art to add N-methyl-2-pyrrolidone as a penetration enhancer. Moreover, even if one were so motivated to add N-methyl-2-pyrrolidone as a solvent to the formulation in Chang, the resulting formulation would not result in a solution since Chang and Konno teach gels or solid formulation respectively. Further, one of ordinary skill in the art would not look to these teachings if one intended to formulate the calcium dihydropyridine antagonist as a solution, let alone the superior results that one obtains when the dihydropyridine calcium antagonists, components that are notoriously difficult to administer transdermally, are formulated in the inventive system. Hence, it is respectfully urged that Chang taken with Konno do not establish a *prima facie* case of obviousness and withdrawal of this rejection is requested.

Claims 1 to 12 stand rejected for allegedly being unpatentable over U.S. Patent 5,045,553 to Ueda et al. ("Ueda") in view of Konno. As Ueda taken with Konno does not teach a TTS wherein the dihydropyridine calcium antagonist is in a solution comprising a specific alcohol, a pyrrolidone derivative and a saturated or unsaturated fatty acid ester of a C_8-C_{16} carboxylic acid and a polyhydric alcohol, the rejection does not establish a *prima facie* case of obviousness and withdrawal of the rejected is requested.

Ueda disclose a pharmaceutical composition for percutaneous drug absorption which comprise the dihydropyridine compound (nilvadipine) as the chief active ingredient and ethanol and or an unsaturated higher fatty acid as a percutaneous absorption promoter in a suspension or suspension gel (see paragraph bridging cols. 2 and 3 or the examples). Hence, Ueda does not disclose solutions.

For the reasons discussed above, Konno does not correct this deficiency as it is directed to solid formulations. Hence, it is urged that neither of these prior publications suggests to one of ordinary skill in the art that one may successfully formulate the dihydropyridine calcium antagonist as a solution and successfully administer it transdermally. Again, it is noted that the art recognizes the fact that active agents are very hard to administer transdermally. Thus, it is urged that the rejection does not establish a *prima facie* case of obviousness and its withdrawal is requested.

Claims 1 to 12 stand rejected for allegedly being unpatentable over EP 680 759 ("EP document") in view of Konno. Again, as the EP document taken with Konno does not teach a solution containing the dihydropyridine calcium antagonist in a specific alcohol, pyrrolidone derivatives and C_8-C_{16} saturated or unsaturated fatty carboxylic acid and a polyhydroxy alcohol,

let alone the superior effects obtained by the inventive formulation, it is urged that the rejection does not establish a *prima facie* case of obviousness. Accordingly, its withdrawal is requested.

This rejection suffers the same deficiencies found in the previous rejections. None of these documents alone or in any fair combination teaches or suggests a solution for a drug reservoir comprising a calcium antagonist of the dihydropyridine type together with a combination of skin permeations enhancer compounds, a pyrrolidone derivative and saturated or unsaturated fatty acid ester of a carboxlic acid containing 8-16 carbon atoms and a polyhydroxy alcohol, dissolved in alcohol would enhance the permeability of the skin to transport of drugs through the skin. Moreover, none of these publications suggests that such a formulation would provide a TTS device that effectively administering drugs of the dihydropyridine type and greatly increasing the drug permeability through the skin, let alone the surprising increase in the transdermal flux of drug. The EP document suffers from the same deficiencies.

The EP document discloses transdermal formulations of DHP calcium antagonists in a mixed liquid comprising cis-oleic acid and dimethylisosorbide dispersed in a propylene glycol base. Example 3 describes reservoirs containing nifedipine as active ingredient suspended in a cosolvent vehicle composed of dimethylisosorbide, oleic acid, ethanol and the main component propylene glycol. As indicated on page 4, lines 41 to 49, the formulations are gels or suspensions and not solutions.

Again, Konno does not correct for this deficiency since it discloses solid or semi-solid formulations, which would teach away from the gels or suspensions in the EP document or the solutions of the present invention. Further, there is no suggestion of the superior results (i.e. transdermal solvent) exhibited by the present invention. Thus, it is urged that the rejection must fail and its withdrawal is requested.

Favorable action is earnestly solicited.

Respectfully submitted,

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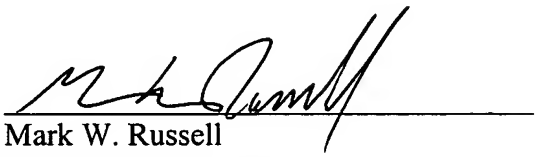
By: 

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